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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/053,530	01/17/2002	Jeffrey A. Ledbetter	390069.401	8993

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EXAMINER	
HELMS, LARRY RONALD	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 01/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/053,530	LEDBETTER ET AL.	
	Examiner	Art Unit	
	Larry R. Helms	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-13,19 and 23-109* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-11,19 and 23-109* is/are rejected.

7)☒ Claim(s) *12 and 13* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Claims 3, 14-18, 20-22 have been canceled.

Claims 4, 10-11, have been amended and claims 23-109 have been added.

2. Claims 1-2, 4-13, 19, 23-109 are under examination.

3. The text of those sections of Title 35 U.S.C. code not included in this office action can be found in a prior Office Action.

4. The following Office Action contains NEW GROUNDS of rejection.

Claim Objections

5. Claims 32-33 are objected to because of the following informalities: The claims need the term "of" after "capable". Appropriate correction is required.

Rejections Withdrawn

6. The rejection of claims 3 and 14 under 35 U.S.C. 112, first paragraph, is withdrawn in view of the amendments to the claims.

7. The rejection of claims 1-2, 4, 7-8, 19 under 35 U.S.C. 102(b) as being anticipated by Bodmer et al (U. S. Patent 5,677,425, issued 10/97) is withdrawn in view of arguments.

8. The rejection of claims 1, 8, 12, 19 under 35 U.S.C. 102(e) as being anticipated by Morrison et al (U.S. Patent 6,284,536, with priority to 4/98) is withdrawn in view of arguments.

9. The rejection of claims 1-2, 4-12 and 19 under 35 U.S.C. 103(a) as being unpatentable over Shan et al (The Journal of immunology 162:6589-6595, 1999, IDS #7) as applied to claims 1-3, 5, 7-11, 19 above, and further in view of Bodmer et al (U. S. Patent 5,677,425, issued 10/14/97) and Morrison et al (U.S. Patent 6,284,536, priority to 4/98) is withdrawn in view of arguments.

10. The rejection of claims 1-2, 4-13 and 19 under 35 U.S.C. 103(a) as being unpatentable over Shan et al (The Journal of immunology 162:6589-6595, 1999, IDS #7) as applied to claims 1-3, 5, 7-11, 19 above, and further in view of Bodmer et al (U. S. Patent 5,677,425, issued 10/14/97), Morrison et al (U.S. Patent 6,284,536, priority to 4/98) and Armitage et al (U.S. Patent 6,264,951, filed 12/96) is withdrawn in view of arguments.

Response to Arguments

11. The rejection of claims 1-2, 4-13, 19, and newly added claim 74 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained.

The response filed 10/28/03 has been carefully considured but is deemed not to be persuasive. The response states that the term "derived" is used in numerous places in the specification and the term refers to changes in amino acids when compared to naturally-occurring polypeptide containing a cysteine residue and "derived" is simply an indication of the number of cysteine residues in the hinge in comparison to the wild-type hinge (see pages 24-25 of response). In response to this argument, the claims require a hinge having, none, one, or two or more cysteines when compared to wild-type, however, the rest of the hinge region is not defined and it is not clear how it is "derived" from the wild-type hinge region.

12. The rejection of claims 1-2, 5, 7-11, 19 and newly added claims 24-28, 31-34, 39, 50-51, 59, 72-74, 78, 82, 84-87, 93-94, 97-98 under 35 U.S.C. 102(b) as being anticipated by Shan et al (The Journal of immunology 162:6589-6595, 1999, IDS #7) is maintained.

The newly added claims encompass single chain molecules that decrease the number of cells in vivo and in vitro and are joined with a linker of at least 6 amino acids and the hinge has one or more cysteine replaced by serines and pharmaceutical compositions comprising such for treatment of malignant B cell disorder, wherein the hinge is a mutated human IgG hinge which as evidenced from Bodmer (US Patent 5,677,425, figure 1, IgG1 has 16 residues) IgG1 reads on this. For this rejection the intended use recited in claim 50 is given no patentable weight.

The response filed 10/28/03 has been carefully considured but is deemed not to be persuasive. The response states that the goal of the reference was to examine the impact of the length of the linker between scFv variable heavy and light chains on binding function (see page 27 of response). In response to this argument, this is immaterial to the 102 rejection. It does not matter what the Authors goal was. They teach the claimed molecules.

The response further states that there is no mention of ADCC activity or complement fixation activity in Shan et al and those skilled in the art would not have expected such a construct to have ADCC and/or CDC activity and the response sites several references to support this as well as case law that a person of ordinary skill in the art must recognize the inherent property (see pages 27-34).

In response to this argument, Shan et al clearly teach the claimed molecules and just because they do not mention the inherent properties does not mean the compound does not have the property. In addition, products of identical chemical composition can not have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. In re Spada 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999) Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999) Atlas Powder Co. V. IRECO, 51 USPQ2d 1943 (Fed. Cir. 1999) "Artisans of ordinary skill may not recognize the inherent characteristics or functioning of the prior art... However, the discovery of a previously unappreciated

property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer. " The Court further held that "this same reasoning holds true when it is not a property but an ingredient which is inherently contained in the prior art". Mehl/Biophile International Corp. V. Milgraum, 52 USPQ2d 1303 (Fed. Cir. 1999)

Thus viewed as a whole, the Polla disclosure shows that the "natural result flowing from the operation as taught would result in alignment of the laser light over the hair follicle, as claimed." This was true even thought Polla did not mention the goal of hair removal. Therefore, the Court held that the '192 patent was invalid as anticipated.

The Courts have held that there is no requirement that those of ordinary skill in the art know of the inherent property. See MPEP 2131.01(d) and MPEP § 2112 - § 2113 for case law on inherency. Also note that the critical date of extrinsic evidence showing a universal fact need not antedate the filing date. See MPEP § 2124.

Therefore the rejection is maintained.

13. The rejection of claims 1, 2, 4-11, 19 and newly added claims 24-28, 31-34, 39, 50-51, 59, 72-74, 78, 82, 84-87, 93-94, 97-98 under 35 U.S.C. 103(a) as being unpatentable over Shan et al (The Journal of immunology 162:6589-6595, 1999, IDS #7) and further in view of Bodmer et al (U. S.Patent 5,677,425, issued 10/14/97) is maintained.

The response states that Shan and Bodmer are quite different and there is no basis to combine (see page 40 of response). In response to this argument, Bodmer teaches humanization of antibodies that are therapeutically relevant in humans and the antigen as taught by Shan is CD20 which is associated with a human cancer and as such it would be obvious to humanize the antibody of Shan. Because the hinge region of Shan does not have any cysteines it would inherently not dimerize. This rejection has been altered and Bodmer is only needed to make up for the teachings lacking in Shan of a human variable region. It would have been obvious to combine Bodmer who teaches humanization with Shan who teaches the antigen CD20 is a cancer antigen in human cancers and it would have been obvious to humanize the antibody of Shan by methods taught in Bodmer and known in the prior art the time of the claimed invention.

The following are NEW GROUNDS of rejections

Claim Rejections - 35 USC § 112

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 52-53, 55-59 are rejected under 35 U.S.C. § 112, first paragraph, because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention, because the

specification does not provide evidence that the claimed biological materials are (1) known and readily available to the public; (2) reproducible from the written description.

It is unclear if a cell line which produces an single chain antibody having the exact chemical identity of L6, HD37, or G28-1 is known and publicly available, or can be reproducibly isolated without undue experimentation. Therefore, a suitable deposit for patent purposes is suggested. Without a publicly available deposit of the above cell line, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. Exact replication of: (1) the claimed cell line; (2) a cell line which produces the chemically and functionally distinct antibody claimed; and/or (3) the claimed antibody's amino acid or nucleic acid sequence is an unpredictable event.

For example, very different V_H chains (about 50% homologous) can combine with the same V_K chain to produce antibody-binding sites with nearly the same size, shape, antigen specificity, and affinity. A similar phenomenon can also occur when different V_H sequences combine with different V_K sequences to produce antibodies with very similar properties. The results indicate that divergent variable region sequences, both in and out of the complementarity-determining regions, can be folded to form similar binding site contours, which result in similar immunochemical characteristics. [FUNDAMENTAL IMMUNOLOGY 242 (William E. Paul, M.D. ed., 3d ed. 1993)]. Therefore, it would require undue experimentation to reproduce the claimed antibody species L6, HD37, G28-1. Deposit of the hybridoma would satisfy the enablement requirements of 35 U.S.C. § 112, first paragraph. See, 37 C.F.R. 1.801-1.809. Deposit of antibody 2H7 is

not needed because the specification teaches the variable light and heavy chain amino acid sequence for the single chain antibody (see Figure 1).

16. Claims 23, 26-109 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Newly added claim 23 recites part (d) in the claim and the response filed 10/28/03 states that support can be found at page 17, 26, Example 6 and original claim 1. At the recited locations the specification teaches in vivo expression of fusion proteins, compositions for preparing immunoglobulin fusion proteins, In vivo studies using 2H7scFvIg, and original claim 1 does not mention this limitation. Therefore, the examiner was unable to apparently locate support for the limitation. Applicant is required to provide specific support for the limitation in the specification as originally filed or remove it from the claim.

17. Claim 53 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 53 has been added and recites the limitation of "wherein said single chain Fv is not a 1F5 single chain Fv". The response filed 10/28/03 did not state where support for the limitation can be found. The Examiner did not apparently find support and as such applicant is required to provide specific support for the limitation in the specification as originally filed or remove it from the claim.

18. Claims 107-108 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Newly added claim 107 recites "capable of binding to CD20 joined to an IgE constant region polypeptide". The response filed 10/28/03 states that support can be found at page 16, lines 5-15. The text at the recited location does not recite anything about IgE constant regions. Therefore, applicant is required to provide specific support for the limitation in the specification as originally filed or remove it from the claim.

Claim Rejections - 35 USC § 103

19. Claims 1, 2, 4-11, 19 and newly added claims 24-39, 50-51, 59-66, 72-74, 78, 82, 84-87, 93-94, 97-98, 106, 109 are rejected under 35 U.S.C. 103(a) as being

unpatentable over Shan et al (The Journal of immunology 162:6589-6595, 1999, IDS #7) and further in view of Kucherlapati et al (US Patent 6,150,584, filed 10/96).

The clams are summarized as a single chain polypeptide with a hinge region with mutated cysteines and the peptide is from a human immunoglobulin and the peptide binds CD20, CD37, CD19, HER2, CD27, CD83, L6.

Shan et al teach a scFv that binds Cd20 that has the recited linker and the cysteines are removed and the hinge is fused to a CH2, CH3 and compositions in buffer and the hinge, CH2 and CH3 were added to facilitate purification. Shan et al does not teach binding of the single chain to antigen other than CD20. This deficiency is made up for in the teachings of Kucherlapati et al.

Kucherlapati et al teach human antibodies to a wide range of therapeutic antigens which are CD's, interleukins, tumor antigens, etc (see column 9-11).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have produced a scFv with a modified hinge, CH2, CH3 as taught by Shan that bound the antigens taught by Kucherlapati et al.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a scFv with a modified hinge, CH2, CH3 as taught by Shan that bound the antigens taught by Kucherlapati et al because Shan et al teach that the human IgG1 hinge, CH2, CH3 was used to facilitate purification and the hinge was modified to produce monomeric scFv-Ig molecules. In addition, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have produced a scFv with a modified hinge,

CH2, CH3 as taught by Shan that bound the antigens taught by Kucherlapati et al because Kucherlapati et al teach many antigens that are useful in human therapy that the antibodies can bind to. Thus, it would have been obvious to produce a modified single chain antigen binding molecule with a mutated hinge, CH2, CH3 as taught by Shan et al and add a Ig region to purify the scFv and produce the molecule to bind any of the therapeutically relevant antigens as taught by Kucherlapati et al. It would also be obvious that the scFv-IgG has ADCC and complement fixation.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

20. No claim is allowed.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 7:00 am to 4:30 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of

this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

22. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879

LARRY R. HELMS, PH.D
PRIMARY EXAMINER